Biol Blood Marrow Transplant 22 (2016) 54–60

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Reducing Treatment-Related Mortality Did Not Improve Outcomes of Allogeneic Myeloablative Hematopoietic Cell Transplantation for High-Risk Multiple Myeloma: A University of Michigan Prospective Series

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Article history:
Received 11 May 2015
Accepted 20 July 2015

Key Words:
Multiple myeloma
Allogeneic
Myeloablative
Reduced toxicity
Prospective
Fludarabine
Busulfan

A B S T R A C T

Despite the ongoing advent of more effective immunomodulators and proteasome inhibitors, multiple myeloma (MM) remains incurable and no effective therapy is available for advanced aggressive disease. Although allogeneic (Allo) hematopoietic cell transplantation (HCT) has a curative potential, the outcomes remain poor because of high treatment-related mortality (TRM), mostly due to regimen-related toxicities and graft-versus-host disease (GVHD) in case of myeloablative conditionings, high relapse rate in case of reduced-intensity or nonmyeloablative regimens, and possibly other unknown MM-specific issues. In an attempt to improve TRM, without compromising conditioning intensity, we prospectively explored the feasibility and efficacy of a myeloablative but reduced-toxicity conditioning regimen, consisting of fludarabine and busulfan (FluBu4; fludarabine 40 mg/m^2/day and busulfan 3.2 mg/kg/day i.v. $\times$ 4 days) in 22 patients with high-risk or advanced refractory MM. The majority (14 of 22, 64%) had prior autologous HCT. The median HCT-specific comorbidity index score was 3 (range, 0 to 6), with 46% having a Karnofsky performance score $<$ 80%. Ten patients had unrelated donors, 3 of whom were 7/8 HLA–loci matched. GVHD prophylaxis was tacrolimus and methotrexate in 20 (91%). Most patients had active MM at transplantation, with a partial response in 12 of 22 (46%) and stable disease in 1 of 22 (4.5%). All 22 patients tolerated the FluBu4 conditioning well, without early toxic deaths or graft failure. Common regimen-related toxicities included mild to moderate mucositis (18 of 22, 82%) and mild transient liver function abnormality (9 of 22, 41%). There were no grade 4 toxicities but grade 3 mucositis occurred in 7 of 22 patients (32%). The cumulative incidence of severe, grades III and IV acute GVHD at day 180 was 23% (95% confidence interval [CI], 10% to 47%) and that of chronic GVHD was 68% (95% CI, 46% to 88%). The cumulative incidences of TRM at 100 days, 1 year, and 3 years were 9% (95% CI, 2% to 33%), 19% (95% CI, 7% to 44%), and 29% (95% CI, 13% to 55%), respectively. Two TRMs were due to idiopathic pneumonia syndrome and 1 was due to cirrhosis. They all had decreased pre-HCT corresponding organ function, with HCT-specific comorbidity index scores of $>$ 3. With a median follow-up of 58.7 (range, 39 to 82) months, the cumulative incidences of relapse at 1 and 3 years were 37% (95% CI, 20% to 61%) and 50% (95% CI, 29% to 75%); those for 1-year and 3-year overall survival (OS) were 58% (95% CI, 40% to 83%) and 29% (95% CI, 15% to 57%), respectively, and those for the 1-year and 3-year progression-free survivals (PFS) were 40% (95% CI, 23% to 67%) and 15% (95% CI, 5% to 42%), respectively. In summary, the use of the myeloablative FluBu4 conditioning Allo-HCT for high-risk MM resulted in decreased TRM, compared with that of Allo-HCT using conventional myeloablative regimens; however, the relapse rate was high, including in those developing moderate-to-severe chronic GVHD. This suggested a less robust graft-versus-myeloma effect against

Financial disclosure: See Acknowledgments on page 59.

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http://dx.doi.org/10.1016/j.bbmt.2015.07.021

high-risk MM, thus resulting in poor PFS and OS. Nonetheless, the FluBu4 regimen may be used as a lower-TRM platform to combine with other strategies, eg, addition of an MM-targeted agent and/or maintenance therapy with these agents, to decrease relapse or progression in patients with high-risk MM.

INTRODUCTION

Multiple myeloma (MM) is a common clonal plasma cell disorder estimated to account for 24,050 new cases and 11,090 deaths in the United States in 2014 [1]. First-line consolidative high-dose therapy and autologous (Auto) hematopoietic cell transplantation (HCT) have been shown to prolong myeloma progression [2-4] and are currently considered a standard of care [5,6]. Although new immunomodulators or targeted agents are now challenging the way we think about the disease and its treatment, MM remains incurable. Moreover, the prognosis is extremely poor in high-risk cases, with a median survival of 8 to 14 months after treatment [7-11].

Allogeneic (Allo) HCT has been explored in advanced MM as a curative option through a graft-versus-myeloma (GVM) effect [12-21]. The existence of a GVM effect was demonstrated after the observation of complete responses (CR) after donor lymphocyte infusion (DLI) and withdrawal of iimmunomodulators in patients with MM relapsing after Allo-HCT [16-18]. Unfortunately, conventional myeloablative conditioning is associated with an unacceptably high early treatment-related mortality (TRM) of up to 50% [12-15]. The use of reduced-intensity regimens to improve TRM in these advanced MMs has not improved overall outcomes, as the relapse rate increased up to 60% [22-25]. The use of upfront tandem reduced-intensity related donor Allo-HCT after Auto-HCT in early-stage MM may be associated with improved progression-free survival (PFS) over single or tandem Auto-HCTs in high-risk MM, but it is not consistently in standard-risk disease [26-32]. The reason for the higher TRM and relapse in Allo-HCT for MM remains unknown, but they have been attributed to multiple factors, including patient age, regimen-related toxicity in case of myeloablative conditionings, a less potent GVM effect, and possibly other poorly understood myeloma-specific factors [13-15,25,33,34].

The myeloablative but reduced-toxicity fludarabine and busulfan (FluBu4) conditioning regimen was shown to be very safe and effective for acute myeloid leukemia and myelodysplastic syndrome, with a regimen-related toxicity of 1%, a TRM of 3%, and a PFS rate of 75% at 1 year [35]. In an attempt to improve outcomes by decreasing TRM without compromising conditioning intensity, we explored the feasibility and efficacy of this myeloablative fludarabine–based Allo-HCT for high-risk or advanced MM. Based on the Consensus Criteria by the Reduced-Intensity Conditioning Regimen Workshop, which was convened by the Center for International Blood and Marrow Transplant Research in 2006, myeloablative regimens ablate marrow hematopoiesis, without spontaneous autologous hematologic recovery, while nonmyeloablative regimens, which cause minimal to moderate cytopenias, do not require hematopoietic stem cell support. Regimens that do not fit the definition for either are classified as reduced-intensity regimens, resulting in potentially prolonged cytopenias and requiring hematopoietic stem cell support [36].

PATIENTS AND METHODS

Between 2008 and 2011, we conducted a prospective study using a myeloablative FluBu4 conditioning followed by an Allo-HCT in 22 patients with measurable disease, high-risk or advanced refractory MM. The protocol was approved by the institutional review board at the University of Michigan Comprehensive Cancer Center. The diagnosis of MM and treatment response evaluation followed the International Myeloma Working Group Guidelines [37,38]. High-risk MM was defined by (1) unfavorable conventional or fluorescence in situ hybridization cytogenetics for t(4;14), t(14;16), t(14;20) and -17p, and by exclusively conventional method for -13 and hypodiploidy, (2) early MM relapse or progression within 12 months after an Auto-HCT. Disease status at transplantation was required to be stable disease or better. The FluBu4 myeloablative conditioning consisted of fludarabine 40 mg/m^2/day i.v. and busulfan 3.2 mg/kg/day i.v., both for 4 days on days -5 through day -2, where day 0 is the day of hematopoietic cell infusion. A busulfan pharmacokinetics study was performed on samples obtained on day -5 in all patients. Busulfan doses on day -3 and day -2 were adjusted accordingly to target the concentration at steady state at 600 to 900 ng/mL. Graft-versus-host disease (GVHD) prophylaxis was tacrolimus starting on day -3 with a targeted trough blood level of 8 to 12 ng/mL and methotrexate 5 mg/kg/day i.v. on days +1, +3, +6, and +11. Tacrolimus was tapered off by day +180 in patients without grades II to IV acute GVHD. Donors were matched or single loci–HLA mismatched related or unrelated. Organ function requirements included serum creatinine $<$ 2.0 mg/dL, serum total bilirubin $<$ 3.0 mg/dL, aspartate and alanine transaminases $<$ 4 times upper limit normal, left ventricular ejection fraction $\geq$ .4, forced expiratory volume and functional vital capacity $\geq$ 40% predicted values, diffusion capacity of the lung for carbon monoxide $\geq$ 40% predicted value, and Karnofsky performance status $\geq$ 70%. *Neutrophil engraftment day* was defined as the first day of the 3 consecutive days of achieving an absolute neutrophil count (ANC) $\geq$ 500/uL. *Platelet engraftment day* was defined as the first day of 2 consecutive days of achieving platelet count $\geq$ 20,000/uL without transfusion support. The revised National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was utilized to report adverse events and toxicities [39]. Acute and chronic GVHD severity grading and classifications followed the 1995 acute GVHD consensus and 2014 National Institute of Health chronic GVHD consensus, respectively [40,41].

Statistical Considerations

Overall survival (OS) and PFS were estimated from the day of transplantation (day 0) and modeled using the Kaplan-Meier method. TRM, graft failure, GVHD, and relapse were estimated using the cumulative incidence method. The study accrued poorly after 3 years of initiation because of competition with other clinical trials of novel targeted agents for advanced MM.

RESULTS

Demographics

A total of 22 MM patients were evaluated and their characteristics are summarized on Table 1. The majority (n = 14, 64%) had a prior Auto-HCT. The median HCT-specific comorbidity index score was 3 (range, 0 to 6) and 10 patients (46%) had a Karnofsky performance score $\leq$ 80%. Twelve patients received grafts from related and 10 from unrelated donors, 7 of which were matched at 8/8 HLA loci and 3 at 7/8 HLA loci. Disease status at transplantation included CR in 3 (14%), very good partial response in 6 (27%), partial response in 12 (46%), and stable disease in 1 (4.5%).

Regimen-Related Toxicity, Engraftment, and TRM

All 22 patients tolerated the myeloablative FluBu4 conditioning regimen well, without early toxic deaths or graft failure. The median times to neutrophil and platelet engraftments were 11 days (range, 10 to 14) and 11 days (range,

Table 1
Patient, Disease, and Transplantation Characteristics and Outcomes

Variable	Value
No. of patients	22
Gender: male/female	14/8
Age at transplantation, median (range), yr	54 (45-70)
Follow-up time, median (range), mo	58.7 (39.5-82)
Myeloma status at transplantation	
CR1	2
CR2/PR1/VGPR1	1/3/1
PR2/VGPR2/SD2	6/5/1
PR3	1
PR4	2
Prior lines of therapy, median (range)	2 (1-4)
Prior autologous transplantation	
None	8 (36%)
1	10 (46%)
2	4 (18%)
Disease risk of relapse	
Low	3 (14%)
Intermediate and high	19 (86%)
HCT-CI score, median (range)	3 (0-6)
Karnofsky Performance Status	
>80%	12 (54%)
≤80%	10 (46%)
Donor	
Related:unrelated	12:10
8/8:7/8 HLA match	17:5
Cell dose, $\times 10^6$ CD34$^+$ cells/kg, median (range)	6.3 (4.4-10.7)
Time to engraftment, median (range), d	
Neutrophil	11 (10-14)
Platelet	11 (0-15)
Regimen-related toxicities	
Gastrointestinal: mucositis	19 (86%)
Grade 1-2	10 (45%)
Grade 3-4	9 (41%)
Hepatobiliary: grade 1-2	13 (59%)
Cirrhosis	1 (4.5%)
Infection: grade 1-2	3 (13%)
Pulmonary (idiopathic pneumonia syndrome): grade 5	2 (9%)
Cumulative incidence of TRM (95% CI)	
At 100 days	9% (2%-33%)
At 1 year	19% (7%-44%)
At 3 years	29% (13%-55%)
Cumulative incidence of GVHD (95% CI)	
Acute GVHD at 180 days	
Grade II-IV	41% (23%-65%)
Grade III-IV	23% (10%-47%)
Chronic GVHD	
At 180 days	41% (23%-65%)
At 1 year	68% (46%-88%)
Cumulative incidence of relapse (95% CI)	
At 100 days	14% (4%-37%)
At 1 year	37% (20%-61%)
At 3 years	50% (29%-75%)
OS (95% CI)	
At 1 year	58% (40%-83%)
At 3 years	29% (15%-57%)
PFS (95% CI)	
At 1 year	40% (23%-67%)
At 3 years	15% (5%-42%)

PR indicates partial response; VGPR, very good partial response; SD, stable diseases; HCT-CI, hematopoietic cell transplantation–specific comorbidity index.
Data presented are n (%), unless otherwise indicated.

0 to 15), respectively. Common regimen-related toxicities (Table 2) included mucositis (n = 18, 82%) and transaminitis (n = 9, 41%). No grade 4 toxicities occurred with the FluBu4 regimen. Seven patients (32%) developed grade 3 oral mucositis. There were no grade 3 abnormal liver functions reported. The cumulative incidences of TRM at 100 days, 1 year, and 3 years were 9% (95% confidence interval [CI], 2% to 33%), 19% (95% CI, 7% to 44%), and 29% (95% CI, 13% to 55%),

Table 2
Adverse Events

Organ System	National Cancer Institute Common Terminology Criteria for Adverse Events		
	Grade 1	Grade 2	Grade 3
Mucositis			
Oral	5	6	7
Colitis			1
Perianal/perineal		1	
Liver function abnormalities			
Transaminitis	9		
Hyperbilirubinemia	3	2	
Elevated alkaline phosphatase	1		
Infection			
Pneumonia			1
CMV retinitis			1
Lips			1
Nausea/vomiting	1		1
Autoimmune thrombocytopenia			1
Urinary tract obstruction			1
Hiccups			1
Acute kidney injury		1	

CMV indicates cytomegalovirus.
Data presented are n.

respectively (Figure 1A). Two TRMs were due to idiopathic pneumonia syndrome and 1 was due to cirrhosis. These patients had decreased pretransplantation corresponding organ function, with HCT-specific comorbidity scores of 3 or higher.

Survival and Relapse

With a median follow-up of 58.7 months (95% CI, 39.5% to 82%), the cumulative incidences of MM progression or relapse at 100 days, 1 year, and 3 years were 14% (95% CI, 4% to 37%), 37% (95% CI, 20% to 61%), and 50% (95% CI, 29% to 75%), respectively (Figure 1B). The OS rates at 1 and 3 years were 58% (95% CI, 40% to 83%) and 29% (95% CI, 15% to 57%), with 1-year and 3-year PFS rates of 40% (95% CI, 23% to 67%) and 15% (95% CI, 5% to 42%), respectively (Figure 2A,B). The causes of death were MM progression in 6 patients (27%), severe organ toxicities in 3 (14%), severe chronic GVHD with/without secondary infection in 3 (14%; 2 GVHDs of gastrointestinal tract and 1 bronchiolitis obliterans), very severe acute GVHD of skin/liver/gastrointestinal tract in 1 HLA-DR mismatched patient (4%), and a late unknown etiology in 1 (4%).

GVHD

Cumulative incidences of grades II to IV and grades III and IV acute GVHD at day 180 were 41% (95% CI, 23% to 65%) and 23% (95% CI, 10% to 47%) (Figure 3A), respectively. Organ-specific staging and overall grading of acute GVHD are shown in Table 3. Most were grades I and II acute skin GVHD (n = 9, 41%) and the most common severe grades III and IV were of the gastrointestinal system (n = 5; 23%). Cumulative incidence of chronic GVHD at 1 year was 68% (95% CI, 46% to 88%) and no events were observed beyond 1 year (Figure 3B). The National Institutes of Health Global Severity Scores for 13 patients with chronic GVHD were mild in 2 (15%), moderate in 5 (39%), and severe in 6 (46%). Of note, one half of patients who experienced chronic GVHD (7 of 13, 54%) developed concurrent or subsequent MM relapse or progression. A majority of these (6 of 7, 86%) were of moderate to high severity scores.

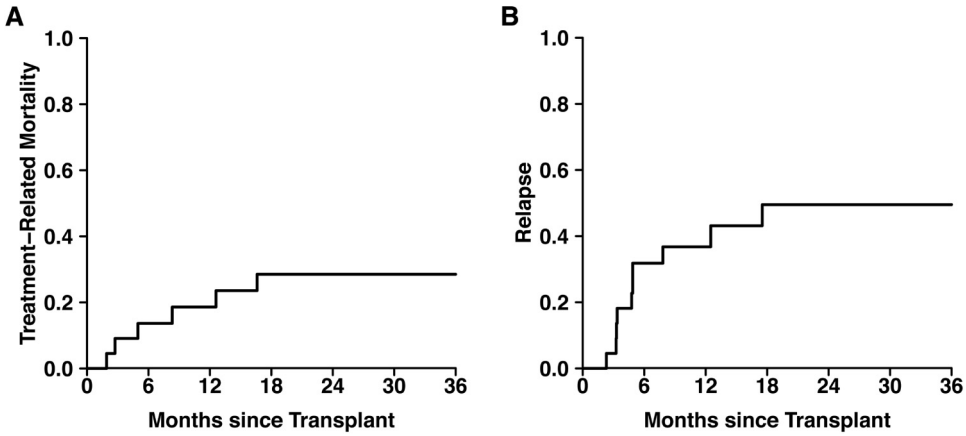

Figure 1. TRM and relapse. The actuarial 3-year cumulative incidences of TRM (A) and MM relapse or progression (B) were 29% and 50%, respectively.

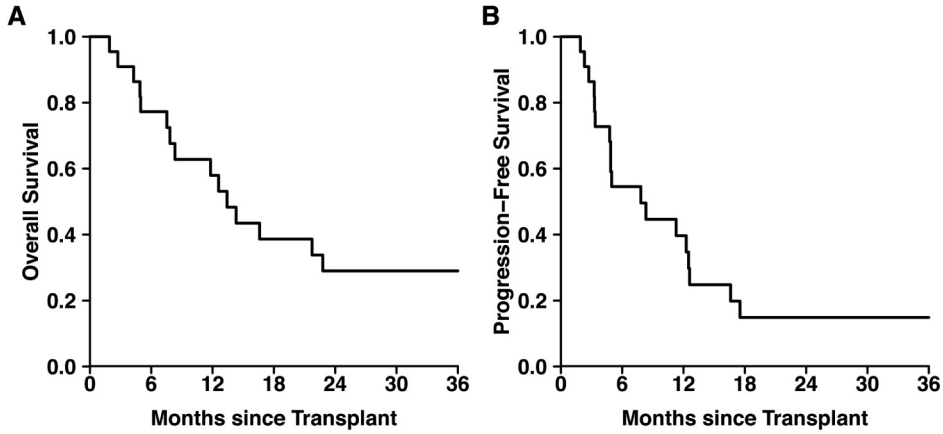

Figure 2. OS and PFS. The actuarial 3-year OS (A) and PFS (B) rates were 29% and 15%, respectively.

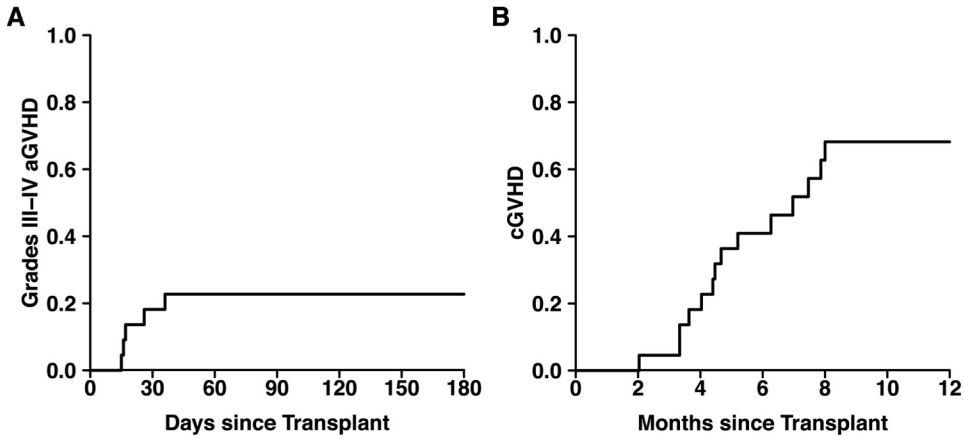

Figure 3. Grade III and IV acute GVHD and chronic GVHD. The actuarial cumulative incidences of grade III and IV acute GHVD at day 180 (A) and chronic GVHD at 1 year (B) were 23% and 68%, respectively.

Table 3
Staging and Grading of Acute GVHD

Organ System	Acute GVHD Stage			
	1	2	3	4
Skin	7	2	1	1
Liver	-	2	-	1
GI tract	3	-	1	4
	Overall Grade			
	I	II	III	IV
	5	5	1	4

GI indicates gastrointestinal.

DISCUSSION

Despite the advent of novel highly potent anti-MM targeted agents, immunomodulators, and proteasome inhibitors, very few effective treatment options are available for patients with advanced relapsed/refractory MM [42]. The treatment outcomes of the triple regimen—bortezomib, lenalidomide, and dexamethasone, which is highly effective for newly diagnosed MM—were very disappointing when used in patients with advanced relapsed/refractory MM (prior number of regimens, 1 to 3). The reported 3-year PFS was 10% [43]. Allo-HCT, which utilizes an alloimmune reaction against MM (GVM effect), has emerged as an alternative treatment option with possible prolonged MM control and curative potential in these patients [12-21]. The existence of the GVM effect was demonstrated directly in patients who received DLI for MM relapse after Allo-HCT [16-18]. DLI was shown to induce complete and partial response in 40% to 55% of these patients, with accompanying acute and chronic GVHD rates of 55% to 57% and 26% to 47%, respectively [16-18]. The response was durable; in the largest series by Lokhorst, the median PFS and OS were 19 and 23 months, respectively [18].

The initial use of myeloablative conditioning resulted in unacceptably high early TRM of up to 40% to 50%; however, a plateau of the long-term MM progression survival curve was demonstrated in those who survived and achieved CR after transplantation, suggesting a cure [12-15]. The attempts to decrease TRM by use of reduced-intensity conditionings, especially the fludarabine/melphalan regimens, were relatively successful. The reported TRM was as low as 10% to 20% but at the expense of the MM relapse rate, which was as high as 80% [22-25]. These findings emphasized the impact of the intensity of the conditioning regimens in controlling MM early after transplantation in patients with advanced refractory disease [22-25].

The use of reduced-intensity Allo-HCT after Auto-HCT (tandem Auto/Allo-HCTs) in patients with newly diagnosed MM according to availability of matched related donors (genetic randomization) initially showed promising outcomes, with improved PFS and OS and without increased TRM [26]; however, subsequent randomized controlled trials (RCTs) enrolling either all comers [30] or only those with high-risk disease [27,28] and the meta-analyses [29,32] of these studies showed no definite benefits. The RCTs in patients with high-risk MM from France (13 deletion or serum beta-2-microglobulin >3 mg/dL) and Spain (achieving less than near CR after Auto-HCT) failed to show any survival benefits of tandem Auto/Allo-HCTs, despite the increased CR rate [27,28]. Compared with the tandem Auto-HCT controls, there was an increase in TRM and CR; however, only a trend toward superior late survival after 36 months in the tandem Auto/Allo-HCT cohort was seen in a subsequent meta-analysis [29]. A more recent RCT in all comers by the European Society for Blood and Marrow Transplantation revealed superior CR and PFS. However, 50% of the control group in this study received only a single Auto-HCT [31]. Lastly, the Blood and Marrow Transplant Clinical Trials Network has reported no benefit of upfront tandem Auto/Allo-HCTs in patients with exclusively standard-risk MM [32].

In an attempt to further improve outcomes by decreasing TRM without compromising conditioning intensity, we studied a myeloablative conditioning regimen consisting of fludarabine and busulfan (FluBu4), which has been associated with reduced regimen-related toxicity [35,44], compared with other conventional myeloablative regimens in patients with high-risk MM.

Our experience concurs with de Lima and Russell groups [35,44]: the myeloablative FluBu4 regimen used in patients with MM is safe and feasible, with a more favorable TRM, comparable to that reported with the reduced-intensity fludarabine/melphalan regimens used in patients with MM [22,23,45] (Table 4). The most common regimen-related toxicities were oral mucositis and transient abnormal liver function tests. Serious and life-threatening toxicities occurred only in those with pre-existing organ-specific comorbidities. The engraftments were early and there were no cases of graft failure. The rates of acute and chronic GVHD were similar to the reported rates for the commonly used reduced-intensity fludarabine/melphalan regimens used in patients with MM [22,23,45] and for the FluBu4 used in patients with acute myeloid leukemia and myelodysplastic syndrome [35,44]. However, the MM relapse/progression rates remained universally high with both fludarabine/melphalan [22,23,45] and the FluBu4 regimen, with a 3-year PFS of 15% in this study. Of note, one half of patients who experienced chronic GVHD concurrently or subsequently developed MM relapse/progression, indicating a less robust GVM effect against high-risk MM. It is also worth noting that the MM relapse rate was remarkably low with the addition of a proteasome inhibitor bortezomib to a reduced-intensity fludarabine/melphalan regimen in the Nishihori series [46], emphasizing the critical role of anti-MM properties in the conditioning in controlling MM relapse/progression. Lastly, chronic GVHD continued to cause significant long-term morbidity and mortality with the use of both fludarabine/melphalan [23,45,46] and the FluBu4 conditioning regimen in this study for MM. Three of 7 (43%) treatment-related deaths were due to severe chronic GVHD.

Nonetheless, our 3-year PFS of 15% is favorably comparable with the 3-year PFS of 10% reported from the aforementioned phase 2 study of combination bortezomib, lenalidomide, and dexamethasone in patients with advanced relapsed/refractory MM [43]. The substitution of bortezomib with carfilzomib in a similar triple regimen; however, improved the 3-year PFS to $\sim$38%, suggesting a critical role of carfilzomib or newer generation proteasome inhibitors in the treatment of advanced MM [47].

In summary, Allo-HCT using the FluBu4 conditioning for high-risk MM appeared to be safe with low TRM. Despite its myeloablative property, however, the relapse/progression rate was unacceptably high and chronic GVHD remained a major contribution to treatment-related morbidity and mortality. This regimen may be used as a novel low-TRM platform for testing additional strategies, such as the addition of a MM-targeted agent with anti-GVHD property (eg, proteasome inhibitors especially carfilzomib or newer

Table 4
Published Series Using Fludarabine-based Allogeneic HCT for MM

Series (Median Age)	n	Unrelated Donor, n (%)	Fludarabine-based Conditioning Regimen	GVHD Prophylaxis	Neutrophil, Platelet Engraftment, median, d	TRM %	Acute GVHD %		Chronic GVHD %	PFS (%)	OS (%)
							Gr II-IV	Gr III-IV			
Giralt [22] (51 yr)	22	9 (41%)	Flu Mel 140 (n = 18) Flu Mel 180 (n = 4)	Tacro MTX	12, 14	100 d, 19; 1 yr, 40	46	27	27	2 yr, 19	2 yr, 30
Shimoni [23] (53 yr)	50	23 (46%)	Flu Mel 100-150 (± ATG)	Tacro MTX	14, 14	5 yr, 26	51	19	63	7 yr, 26	7 yr, 34
Bashir [45] (52, 53 yrs)	23	2 (9%)	Flu Mel 100 (± ATG)	Tacro	12, 12.5	1 yr, 13	25	4	48	2 yr, 41	2 yr, 63
	27	12 (44%)	Flu Mel 140 (± ATG)	MTX Rituximab	12, 13	1 yr, 15	44	22	29	2 yr, 24	2 yr, 45
Nishihori [46] (49, 54 yrs)	22	13 (59%)	Flu Mel 140 ± bortezomib	Tacro-based	15, 16	2 yr, 17	45	Not reported	46	2 yr, 75	2 yr, 78
Current study (54 yr)	22	10 (45%)	Flu Bu 4	Tacro, MTX	11, 11	100 d, 9; 1 yr, 19; 3 yr, 29	48	23	55	3 yr, 15	3 yr, 33

Flu Mel indicates fludarabine/melphalan; Flu Bu, fludarabine/busulfan; ATG, anti-thymocyte globulin; Tacro, tacrolimus; MTX, methotrexate.

agents) and/or maintenance therapy with these agents to decrease relapse/progression in patients with high-risk MM. A randomized phase 2 study of maintenance ixazomib, an oral proteasome inhibitor, after Allo-HCT for high-risk MM is under development by the Blood and Marrow Transplant Clinical Trials Network [48].

ACKNOWLEDGMENTS

Otsuka America Pharmaceutical provided financial support for the study (University of Michigan IC Pilot CIOF 091307).

Financial disclosure statement: None of the authors has any primary financial relationship with Otsuka America Pharmaceutical, which provided financial support to the study (University of Michigan IC Pilot CIOF 091307).

Conflict of interest statement: A.P., S.M., and Y.K. received research funding from Otsuka America Pharmaceutical.

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